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14. ABSTRACT
Lymphedema is a common, chronic, and potentially devastating complication of primary breast cancer therapy. Radiation increases patients' lymphedema risk up to 36% as conventional fields irradiate vital lymphatic tissues. Fusion imaging technologies that combine anatomical and physiological data, e.g. SPECT/CT, may identify lymphatics critical for arm drainage and allow the creation of conformal radiation treatment fields that minimize the exposure of lymph nodes (LNs) and vessels while delivering therapeutic doses to target tissues. This study uses SPECT/CT scanning to localize lymphatics critical for arm drainage, and has established the feasibility of fusing SPECT/CT images with the CT scans used for radiation planning, thereby creating the opportunity to spare essential LNs needless radiation. Further, precise quantification of the dosimetry delivered to LNs draining the arm has revealed harmful levels of incidental irradiation with tangent beam configurations and subtherapeutic exposure with 4-field configurations. Data collection is complete, however interpretation and analysis of follow up SPECT/CT scans is ongoing. Data analysis will address the hypothesis that increased arm volume correlates with high levels of radiation dosimetry delivered to the LNs draining the arm. Additionally, data analysis will determine whether the radiation dose delivered to specific LNs is inversely correlated with radiolabeled tracer uptake, a surrogate measure for functional status, on follow up scans. The proposed study realizes the BCRP goals by elucidating a novel means of refining breast cancer treatment minimize patients' risk of developing the most prevalent and dreaded complication of conventional therapy, lymphedema.

15. SUBJECT TERMS
Lymphedema, Radiation Therapy, Survivorship, Prevention, Lymphoscintigraphy, Breast Cancer

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Introduction:

The aims of this career development award are two-fold and involve training the recipient, Dr. Cheville, in the conduct of responsible research as well as completion of a prospective cohort study to determine whether radiation delivered to the lymph nodes (LNs) that drain the arm engenders lymphedema (LE). LE is considered the number one survivorship issue by breast cancer patients.[1] Affected patients experience diminished quality of life and are more likely to develop social, vocational, psychological and functional decline.[1-4] Imaging approaches that integrate physiological and anatomical data, e.g. SPECT/CT scanning, may permit the precise localization of LNs critical for arm draining after axillary surgery.[5] Successful fusion of SPECT/CT images with the CT scans used in radiation planning creates the opportunity to quantify radiation doses delivered to specific LNs and to create image-guided treatment configurations that might spare these LNs. Further, quantification allows empiric testing of the hypothesis that increased radiation exposure correlates with a higher incidence of lymphedema.[6] Testing this hypothesis and fusing SPECT/CT and radiation planning CT scans are requisite <u>initial</u> steps in determining whether image-guided radiation planning may play a wider roll in reducing patients' LE risk.

Thus far, Dr. Cheville's team has succeeded in manual fusion of SPECT/CT and radiation planning CT scans as well as dosimetry quantification. Completion of the proposed work was interrupted by Dr. Cheville's transition from the University of Pennsylvania Health System to the Mayo Clinic, Rochester, MN, and by her maternity leave. Additional delays arose from unanticipated difficulty recruiting patients and fusing SPECT/CT images with the radiation planning CT scans due to DICOM software incompatibility. Nonetheless, the team was able to manually determine spatial coordinates of LNs draining the arm on SPECT/CT scans and to apply these coordinates to the radiation planning CT scans. Thus precise quantification of the LNs radiation exposure was achieved. This achievement is novel with important treatment implications, however the study's original aims have yet to be fulfilled and hypothesis testing is pending completion of data analysis. Data collection is now complete as described in the body of this report.

Although a source of delay, Dr. Cheville's transition to the Mayo Clinic has also created exciting opportunities to realize the study's goals and to expand them. Concurrent with submission of this report, Dr. Cheville has requested a no-cost grant extension to further the study's aims with residual funds by incorporating new technological advances into the original study design. Meaningful technological progress has occurred since the project's inception with important consequences for this work. The latest generation of SPECT/CT scanners and enhanced radiation treatment capacity can be incorporated into continuation of the work at the Mayo Clinic thereby potentiating the projects' goal of substantially reducing breast cancer patients' risk of developing LE. Relevant Mayo Clinic-based assets include;

1. Enhanced DICOM software which will allow computer-based fusion of SPECT/CT scans and CT scans generated for radiation simulation.
2. A new generation Phillips Precedence SPECT/CT scanner which produces high resolution anatomic images that allow precise localization of physiologically important structures, e.g. LNs.
3. Commitment by the clinical staff within the Department of Radiation Oncology for intensive and coordinated patient recruitment.
4. Availability of dedicated treatment planning workstations and 10% effort of a radiation physicist in the Department of Radiation Oncology to develop SPECT/CT-informed radiation treatments.

These unique assets will allow the rapid generation of actionable data and clinical deliverables. In order to take full advantage of these circumstances and to make up for the disappointing recruitment rates at the University of Pennsylvania Health System, Dr. Cheville has obtained approval to recruit additional breast cancer patients at the Mayo Clinic into the protocol outlined in her original proposal. Significantly more up-to-date imaging techniques and radiation planning capacity will be utilized. The proposed project will collect critical data which was inaccessible at University of Pennsylvania Health System due to logistical and technological barriers that were unforeseeable during the project's early planning stages, namely:

1. The inability to perform successful computer-based fusion of SPECT/CT and radiation planning CT images due to DICOM software incompatibility between the Departments of Nuclear Medicine and Radiation Oncology.
2. The sole availability of a low resolution GE Hawkeye SPECT/CT scanner.
3. Lack of dedicated resources to quantify alterations in lymph node dosimetry achievable through SPECT/CT-informed planning.

By expanding the research initiated at the University of Pennsylvania Health System through additional subject recruitment at the Mayo Clinic the following goals can be realized:

1. Refinement of the imaging techniques required for optimal computer-based fusion
2. Demonstration of the infrastructure and processes required for successful execution of a large-scale interventional trial.
3. Precise quantification of the reduction in lymph node radiation exposure achievable through SPECT/CT-based alteration of both conformal radiation tangents and IMRT treatment plans
4. Formulation of recruitment strategies targeting minorities and other potentially under-represented subgroups.

Body:

Task 1. Complete course work and a thesis for a Masters of Science degree in clinical epidemiology and the University of Pennsylvania Center for Clinical Epidemiology and Biostatistics.

Status: Completed

Dr. Cheville, was awarded the degree of Master of Clinical Epidemiology on May 15, 2006. Dr. Cheville's thesis was substantially edited and reduced in length to meet the publication requirements of current cancer journals. The resultant article, "Prevalence and treatment patterns of physical impairments in patients with metastatic breast cancer" was published as the lead article in the June 1st edition of the Journal of Clinical Oncology (J Clin Oncol. 2008 Jun 1;26(16):2610-1.).

Task 2. Conduct a prospective cohort study to estimate the risk of lymphedema associated with radiation dosimetry to lymph node critical for arm drainage. (Months 1-36)

Status: Subject enrollment and data collection are complete. Data, predominantly SPECT/CT images, have been completely transferred from the University of Pennsylvania to the Mayo Clinic. SPECT/CT scan interpretation, completion of data entry, data analysis, and manuscript preparation remain outstanding tasks. Dr. Cheville is currently applying for a no cost extension. The application includes a revised state statement of work with an updated timeline for this task which can be reviewed in Appendix A of this report.

a. Subject enrollment

Thirty seven subjects enrolled in the study. As mentioned in previous reports, this is 13 subjects less than the initial recruitment goal of 50 subjects. Subject recruitment was delayed by the need for approval from multiple regulatory bodies and by the need to determine the optimal amount of radiolabeled tracer for subdermal injection, upper extremity injection sites, and time interval between tracer injection and SPECT/CT scanning. An interim power analysis with updated variance data indicates that with 37 subjects and a two-sided α of .05, there is adequate power to detect a 4.7% difference in inter-limb volume which is below the minimal volumetric criteria for lymphedema on any existing scale. With adequate power, concern over the risk and burden of SPECT/CT scanning in the face of little associated personal benefit for subjects, and Dr. Cheville's imminent transition from the University of Pennsylvania to the Mayo Clinic a decision was made to end recruitment at 37 subjects.

b. Data collection

Follow-up SPECT/CT scans have been obtained a minimum of 12 months following radiation therapy on 32 subjects. The 5 remaining subjects are not available for scanning due to study withdrawal or death. Collection of subjects' demographic, breast cancer and treatment information is complete.

c. SPECT/CT Scan Interpretation

All pre-radiation SPECT/CT scans have been carefully reviewed by a panel of clinicians and scientists expert in lymphoscintigraphic interpretation. Follow-up SPECT/CT scans, $\geq$ 12 months post-radiation, have been completed for all available subjects. However, only 4 follow-up scans have been extensively interpreted. A proposed schedule for complete SPECT/CT scan interpretation is outlined in Appendix A.

d. Data Entry

Data entry is complete with regards to variables pertaining to subjects' pre-radiation SPECT/CT scans, demographics, breast cancer, and treatment. Additional data entry is required for variables pertaining to follow-up SPECT/CT scans and all arm volumes measured >12 months following radiation treatment. A proposed schedule for completing this work is included in Appendix A.

e. Data Analysis

Data analysis is complete for subjects' demographic-, cancer treatment- and pre-radiation SPECT/CT scan-related information. Summary statistics describing the 32 subjects for whom complete data are available are listed in table 1.

Age Mean (SD)	55.3 (15.3)
Ethnicity N (%)	
Caucasian	16 (50.0%)
Afro-American	14 (43.8%)
Hispanic	2 (6.25%)
Body Mass Index Mean (SD)	28.2 (5.7)
Side of cancer N (%)	
Right	17 (53.1%)
Left	15 (46.9%)
Surgery for 1° breast cancer N (%)	
Lumpectomy	18 (56.3%)
Mastectomy	14 (43.8%)
Axillary surgery N (%)	
Sentinel lymph node biopsy only	16 (50.0%)
Axillary clearing	16 (50.0%)
Number of axillary LN resected Mean (SD)	
Total Cohort	8.7 (7.5)
Sentinel lymph node biopsy only	2.8 (1.5)
Axillary clearing	14.6 (6.3)
Chemotherapy* N(%)	19 (59.4%)
Hormonal therapy† (N%)	6 (18.8)%
Elapsed interval between tracer injection and SPECT/CT scan N (SD)	323.1 (46.7) min

Table 1. Demographic and cancer treatment characteristics of the study cohort who completed 2 SPECT/CT scans.
* 3 subjects received Adriamycin & Cytoxan alone while 16 subjects received Adriamycin & Cytoxan followed by a taxane.
† All 6 subjects were taking Arimidex
SD, Standard Deviation; LN, Lymph Node

Details regarding subjects' pre-radiation SPECT/CT scans are listed in Table 2. The number of lymph nodes (LNs) visualized ranged from 1-10 with a mean of 3.4 LNs/patient distributed through out axillary and supraclavicular LN beds.

		Type of Axillary LN Surgery		
	All Subjects	Sentinel LN Biopsy	Multi-level Axillary LN Clearing	
	N=32	N=16	N=16	p value*
	Mean (SD)	Mean (SD)	Mean (SD)	
Total number of visualized LNs	3.4 (2.0)	2.9 (1.5)	3.8 (2.4)	NS†
Number of visualized LN by anatomic location:				
Lateral axilla	1.4 (1.1)	1.6 (1.0)	1.2 (1.2)	NS†
Medial axilla	1.0 (1.1)	0.9 (1.2)	1.0 (0.9)	NS†
Supraclavicular LN bed	1.1 (1.4)	.4 (0.8)	1.9 (1.5)	0.006†
Percentage of total visualized LNs by anatomic location:				
Lateral axilla	47.7%	62.9%	31.6%	0.01†
Medial axilla	26.8%	26.5%	27.1%	NS†
Supraclavicular LN bed	25.5%	10.6%	41.3%	0.005†

Table 2. Results of SPECT/CT scan analyses including mean LN number and relative distribution across anatomic sites for all subjects and subgroups defined by axillary surgical technique.
* p values ≤ 0.1 were reported, otherwise they are listed as non-significant (NS)
† p values are for comparisons of subjects who underwent sentinel LN biopsy versus axillary clearing
‡ p value for a test for trend across ordered groups. The significant p value indicates that

The distribution of visualized LNs by anatomical location is illustrated in figure 1. The "lateral axilla" roughly corresponds to the region containing Level I LNs for surgical

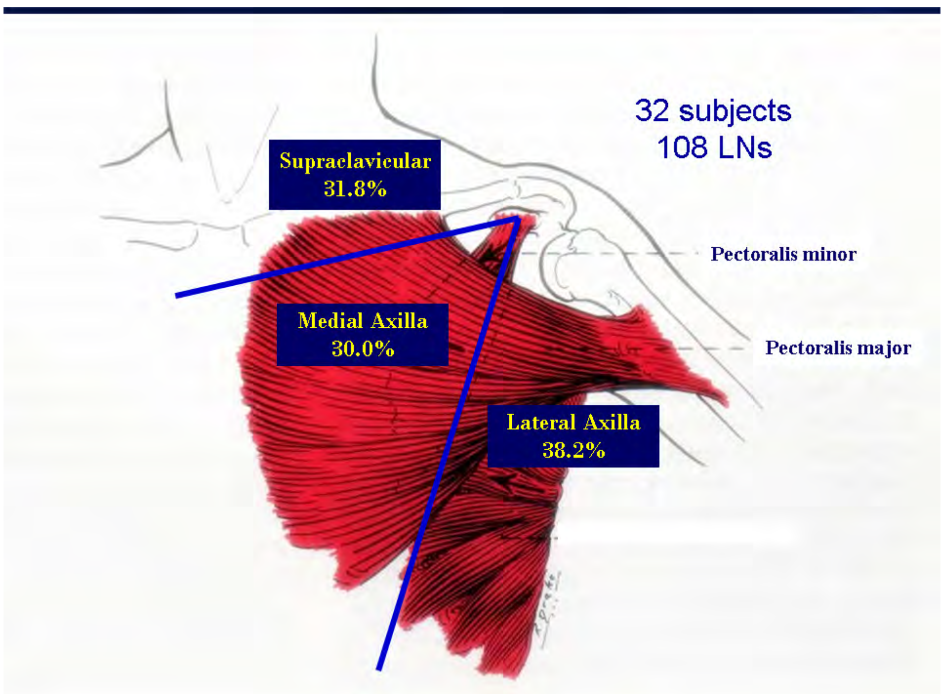

Figure 1.

dissection purposes. The "medial axilla" roughly corresponds to Level II and III LNs. Radiation dosimetry calculations in the 32 subjects with follow-up SPECT/CT scans are complete and indicate that the LNs draining the arm frequently receive the full prescribed radiation isodose (46 – 50 Gy) irrespective of location. Mean radiation dose by LN location is listed in figure 2.   This information is further broken down by radiation dose

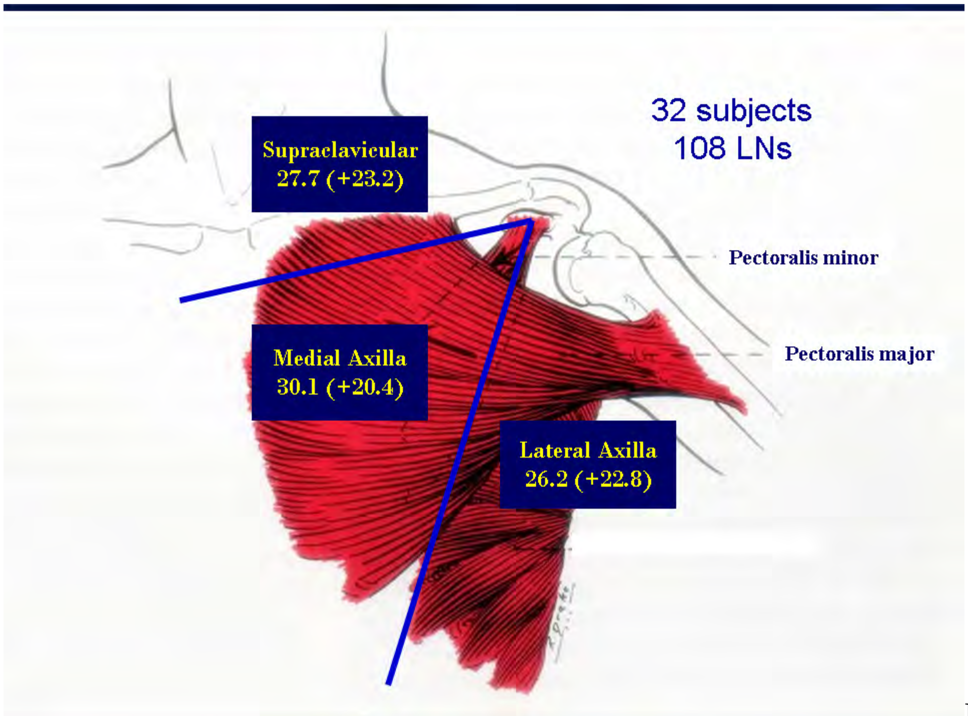

Figure 2

in Gy in Table 3. Figure 2 lists average dosimetry by anatomical location, but makes no distinction by radiation planning technique, e.g. tangents versus 4 field. This distinction is highly relevant since it reflects differing treatment intent. Tangent beams are

Radiation Dose in Gy	LNs	Subjects	Number of LN per location	
>50	10	6	Lat Ax	4
			Med Ax	2
			SC	4
41-50	47	21	Lat Ax	17
			Med Ax	16
			SC	14
31-40	3	2	Lat Ax	0
			Med Ax	2
			SC	1
21-30	2	2	Lat Ax	0
			Med Ax	2

			SC	1
11-20	3	3	Lat Ax	2
			Med Ax	0
			SC	1
0-10	43	19	Lat Ax	17
			Med Ax	11
			SC	15

Table 3. Number of lymph nodes, subjects, and lymph nodes by area grouped by radiation exposure in 10 Gy intervals.

an adjuvant modality delivered to eradicate residual tumor cells from the breast, particularly the primary tumor site. Radiation delivered to axillary or supraclavicular LNs by tangent beams is incidental as LNs are not deliberately targeted by this treatment configuration. In contrast, 4-field radiation is delivered to patients at high risk for local breast cancer recurrence and specifically targets the axillary and supraclavicular LN beds in order to purge these fields of any residual tumor cells. Figure 3 - 5 are 3 histograms which illustrate the radiation dose delivered to visualized LNs with tangent beam, 3-field, and 4 field configurations. The Y-axis of each figure is the percentage of total visualized LNs receiving a particular XRT dose while the X-axis is radiation does in Gy. The percentage of LNs receiving > 40Gy is separately listed in each figure since this is a treatment level associated with lymphatic compromise.

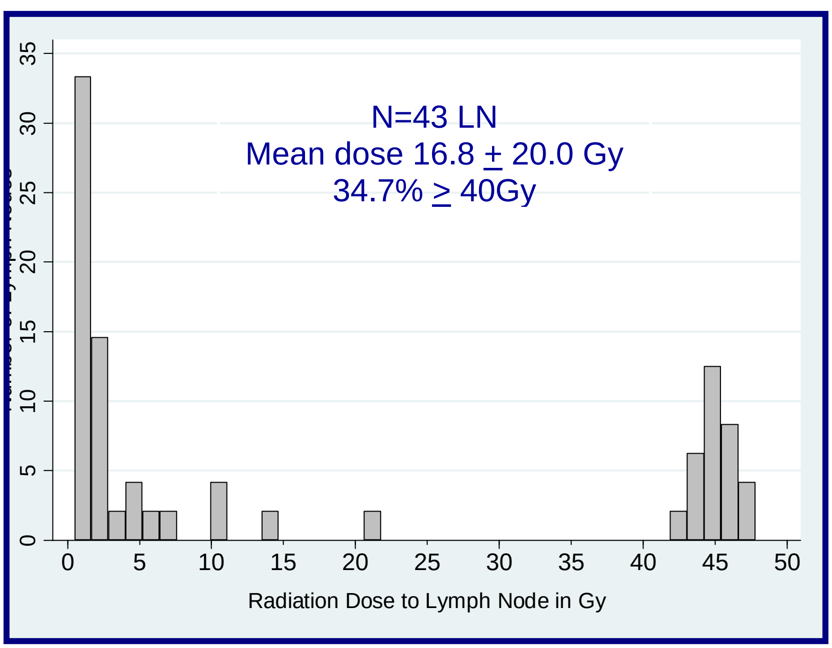

Figure 3. Radiation dose delivered to LNs visualized on SPECT/CT scans and treatment with tangent beam configurations

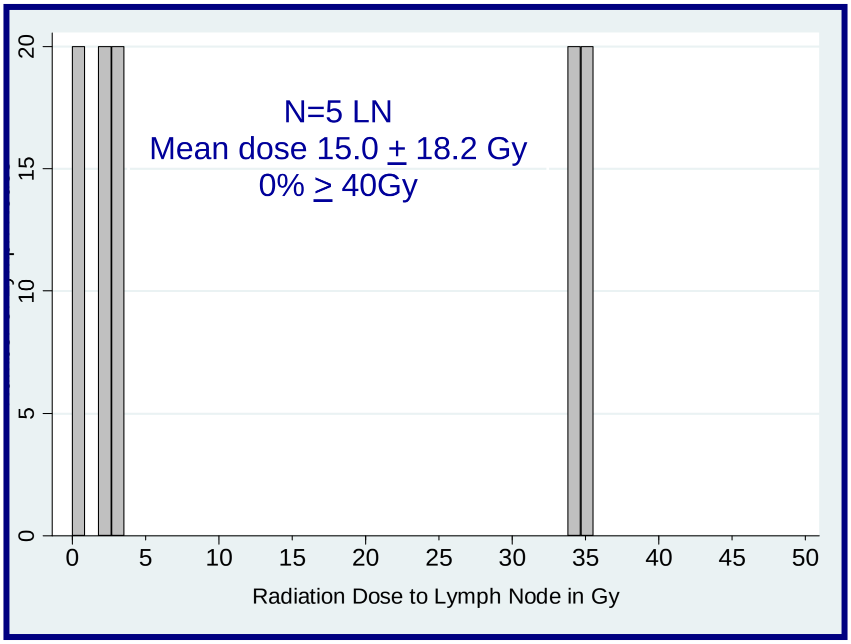

Figure 4. Radiation dose delivered to LNs visualized on SPECT/CT scans and treatment with 3 field configuration (tangent beams + supraclavicular LN irradiation)

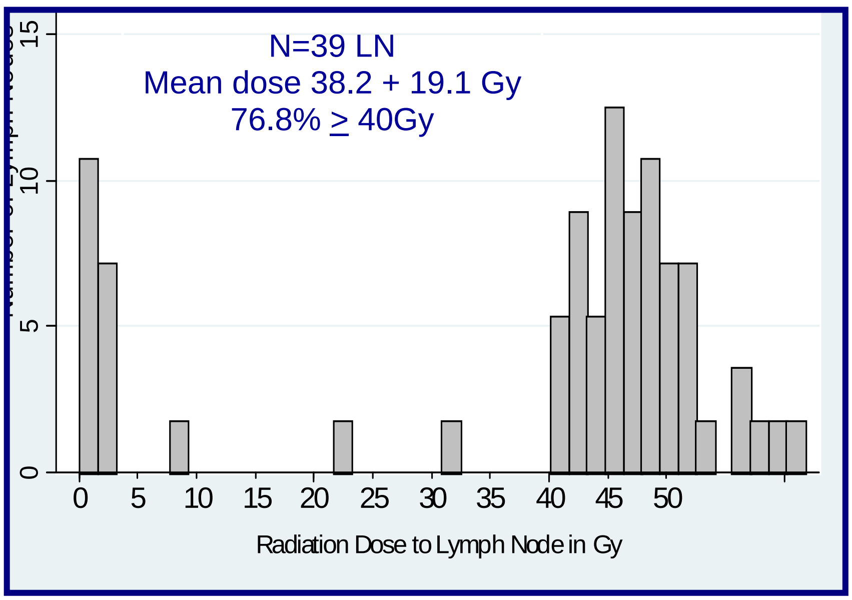

Figure 5. Radiation dose delivered to LNs visualized on SPECT/CT scans and treatment with 4 field configuration (tangent beams + Posterior Axillary Beam + supraclavicular LN irradiation)

The histograms in figures 3-5 demonstrated 2 important and novel findings. First, over 1/3 of LNs critical for arm drainage received ≥40 Gy of incidental radiation with tangent beam configurations. Incidental irradiation adds minimal if any benefit with respect to loco-regional cancer control since these patients are at virtually no risk of axillary recurrence. A significant proportion of this needless and destructive incidental irradiation may be prevented through image-guided conformal radiation planning. Second, up to 42.9% of visualized LNs treated with 4-field configuration received less that the recommended dose of 45 Gy. 4-field beam configurations deliberately target

LNs with the intention of delivering a therapeutic adjuvant dose of >45Gy to all LNs. These data indicate a high prevalence of subtherapeutic radiation dosimetry to LNs targeted with 4-field beam configurations. LNs receiving subtherapeutic radiation doses were distributed equally across anatomic locations; 37.5% lateral axilla, 29.2% medial axilla, and 33.3% supraclavicular bed. SPECT/CT scanning can be utilized to target LNs at risk for harboring metastases. LNs draining the chest wall could be localized with SPECT/CT scanning and adequate dosimetry could be ensured through image-guided precision radiation planning.

To date, consensus interpretation has been completed on only 4 of 32 follow-up SPECT/CT scans. However, the results shed light on what may be an exciting future path to lymphedema prevention. Figures 6 & 7 show pre-radiation and follow up SPECT/CT scans for 2 subjects. Three supraclavicular LNs were visualized in the pre-

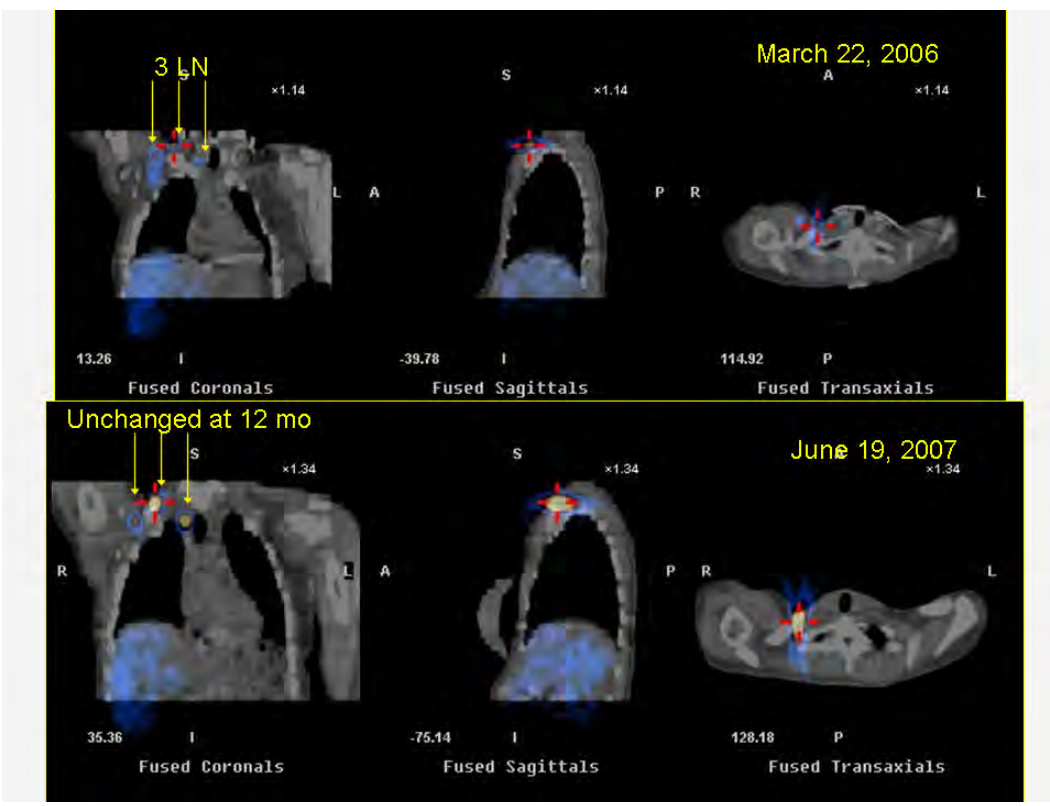

Figure 6. Pre-radiation and follow-up SPECT/CT scan

radiation scan; March 22nd, 2006 in figure 6. The same three nodes appear to be present without significant change in relative tracer uptake on the follow-up SPECT/CT scan; June 19th, 2007. A similar pattern is noted in figure 7 in which a single LN was visualized on the pre-radiation SPECT/CT scan; March 8, 2005, and appears unchanged

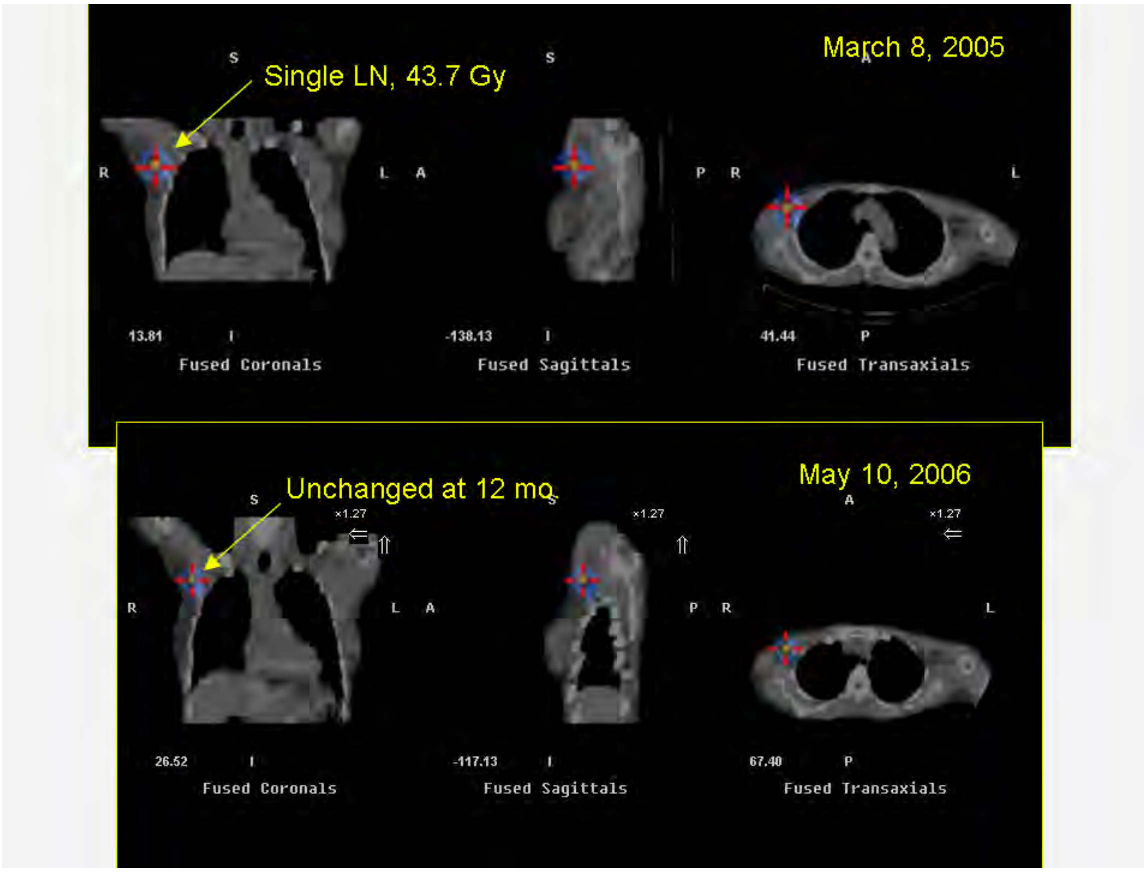

Figure 7. Pre-radiation and follow-up SPECT/CT scan

on the follow-up SPECT/CT scan; May 10, 2006. Figures 8 & 9, however, show a strikingly different pattern. Ten LNs were noted on the pre-radiation scan of the subject in figure 8, while only 3 LNs remain 19 months later on the subject's follow up scan. All of the 3 remaining LNs were visualized on the pre-radiation SPECT/CT scan, suggesting that collateralization has been refined to a lesser number of dominant pathways. Of note, this subject has developed very mild lymphedema that remains under good control only with intermittent use of a compression garment. Figure 9 similarly demonstrates change between pre-radiation and follow-up SPECT/CT scans, but the number of visualized LNs has increased from 4 to 6. Unexpectedly, 3 of the 6 LNs were visualized contralateral to

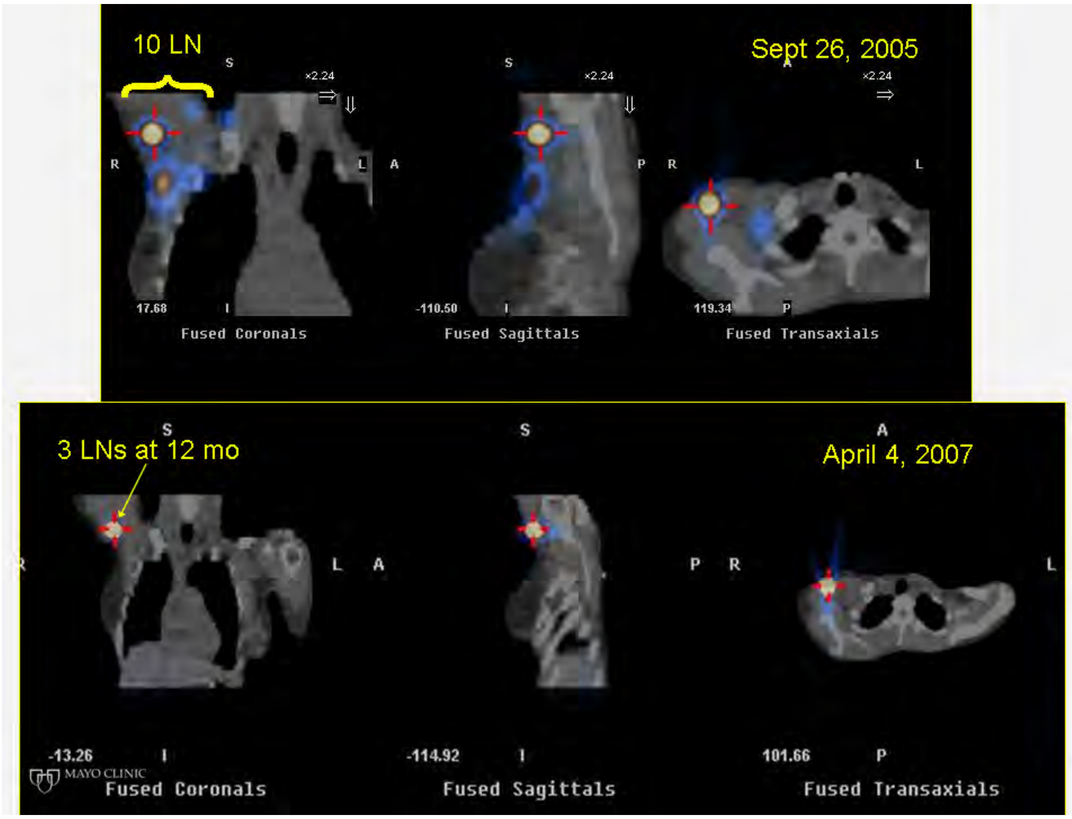

Figure 8. Pre-radiation and follow-up SPECT/CT scan

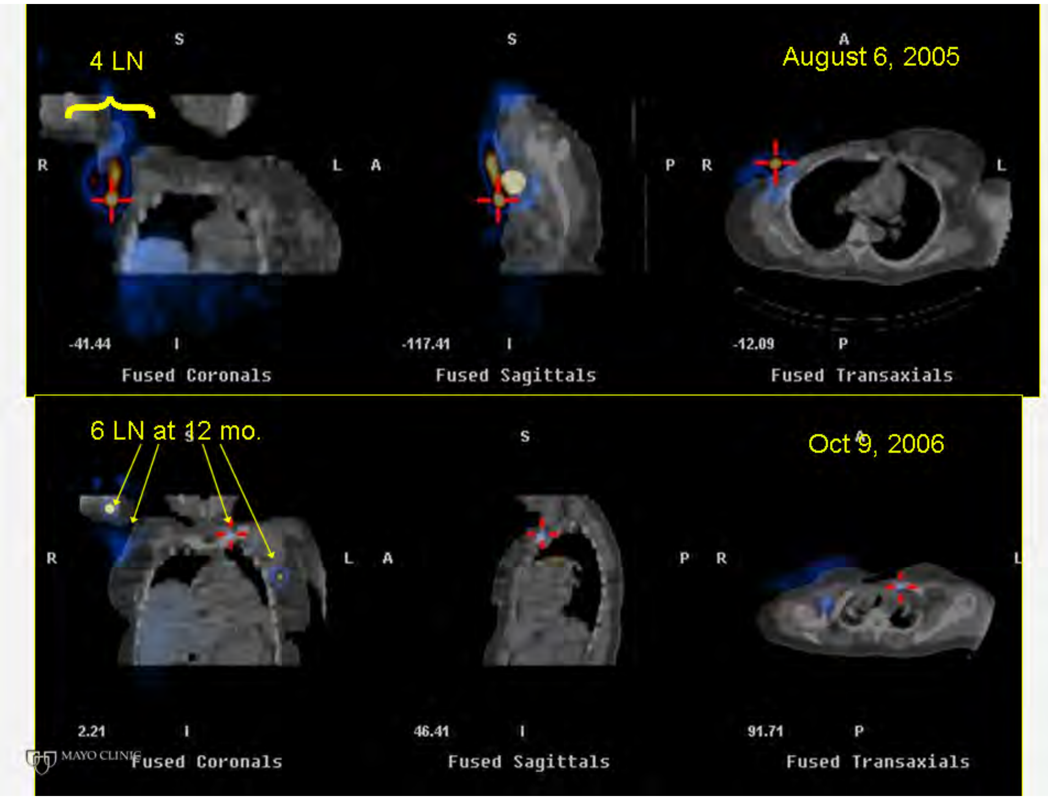

Figure 9. Pre-radiation and follow-up SPECT/CT scan

side of breast cancer treatment. While collateralization and lymphatic reorganization of this extent has been theorized, it has never been demonstrated. Figures 8 & 9 definitively show continued reorganization of the lymphatic system. Since the scans were obtained 19 months apart in Figure 8 and 14 months apart in Figure 9, the time course of collateralization must remain speculative. Collateralization may have been completed during or shortly following radiation. Alternatively reorganization may continue well beyond the time of the follow-up scan.

The mechanism by which the lymphatic system compensates for lymph node loss remains obscure. Our results suggest that collateral drainage pathways involving multiple LNs develop after surgical disruption of the congenital drainage pathways. This finding is clinically relevant since it supports the need to develop interventions that enhance lymphatic collateralization during and after primary breast cancer treatment.

f. Manuscript Preparation

The results of this study are relevant to audiences from different medical disciplines including nuclear medicine, radiation physics and oncology, and lymphology. For this reason three manuscripts with separate emphases have been prepared. The first establishes proof of concept for SPECT/CT fusion imaging to precisely localize LNs draining the arm after breast cancer surgery. This manuscript has been accepted for publication by *Clinical Nuclear Medicine* pending revisions. The second manuscript reports incidental radiation doses delivered to

LNs critical for arm drainage with tangent beam configurations. Further, the paper reports subtherapeutic dosimetry delivered to LNs deliberately targeted with 4-field radiation treatment configurations. The third manuscript describes evidence of lymph collateralization following surgical resection of axillary nodes. This manuscript has been submitted to …

Task 3. Conduct a pilot study of 30 breast cancer patients requiring tangent beam breast irradiation in order to estimate the reduction in LN dosimetry achieved with SPECT/CT-informed standard, SPECT/CT-informed intensity modulated, and standard radiation treatment planning. Substantial residual funds in the project budget coupled with important advances in the fusion imaging field create the possibility of advancing this work and establishing its immediate clinical relevance. Task 3 will further refine the fusion imaging approach developed through Dr. Cheville's previous work by utilizing a new generation, high resolution SPECT/CT (Phillips Precedence) scanner and by employing computer-based image fusion. Task 3 will definitively address barriers to the integration of SPECT/CT-informed imaging into routine clinical practice.

Status: The study has been approved by the Mayo Clinic Cancer Center Protocol Committee and Internal Review Board. All study forms have been developed and approved. All requisite personnel are currently available with time allocated to the project and have been appropriately trained.

Key Research Accomplishments

1. Development of a scintigraphic mapping strategy involving 2-site subdermal injection of technetium labeled sulfur colloid to identify all axillary and supraclavicular LNs essential for arm drainage after surgical axillary LN removal for primary breast cancer.

2. Precise anatomic localization of LNs draining the arm using dual-head Millennium VG gamma camera (GE Healthcare, Waukesha WI) with Hawkeye single-slice CT to generate fusion SPECT/CT images.

3. Manual fusion of GE Hawkeye SPECT/CT scans with CT simulation scans used for radiation planning.

4. Quantification of radiation dosimetry delivered to LN essential for arm drainage with tangent, 3-field, and 4-field beam configurations.

5. Construction of individually tailored standard radiation fields that minimize incidental dosimetry to the LNs draining the arm while delivering therapeutic doses to target tissues.

6. Discovery of the evidence supporting lymphatic collateralization following surgical removal of LNs that may continue as long as 19 months after surgery.

Reportable Outcomes

1. Platform presentation at the American Society of Nuclear Medicine. June, 2006

2. Poster presentation at the annual European Society of Therapeutic Radiation Oncology conference October, 2006.

3. Platform presentation presented to the National Lymphedema Network meeting in November, 2006.

4. Platform presentation at the European Society of Therapeutic Radiation Oncology meeting in Barcelona, Spain September, 2007, *SPECT/CT Imaging in Breast Cancer for Temporal Response of Arm Edema.*

5. Manuscript accepted by Clinical Nuclear Medicine entitled *Novel SPECT/CT-based Lymph Node Imaging Technique in Patients with Breast Cancer: Implications for Preventing Arm Lymphedema following Radiation Therapy.*

6. Manuscript in review entitled *Incidental and Subtherapeutic Lymph Node Dosimetry with Conformal Field Configuations* to Radiotherapy and Oncology.

7. Manuscript in review entitled *The Role of Collateralization in Restoring Lymphatic Homeostasis After Breast Surgery* to Lymphatic Research and Biology

Conclusion

Work to date has established that LNs draining the arm after surgical manipulation of the axilla in the context of primary breast cancer can be localized using SPECT/CT scanning. The radiation dose delivered to LNs can be quantified by manually fusing SPECT/CT images with radiation simulation CT scans. This work creates a foundation for creating image-guided conformal radiation fields that minimize dosimetry to the LNs draining the arm. Customized radiation fields may be safely considered for patients with ‘low risk’ breast cancers (e.g. small tumor, hormone receptor positive, benign histopathological characteristics, and negative sentinel LNs). There are sound theoretical reasons to believe that reduced LN dosimetry will lower patients’ risk of developing lymphedema. Complete data analysis will allow empiric evaluation this association. The fact that more LNs were visualized, particularly in the medial axillary and supraclavicular regions, in patients who underwent completion axillary lymph node dissection suggests that lymph collateralization is an important means of re-establishing lymphatic homeostasis. The dramatic changes in LN drainage patterns noted on twelve month follow up scans adds further support to the importance of collateralization. These findings justify the development of techniques to enhance this endogenous compensatory mechanisms.

Dr. Cheville’s transition to the Mayo Clinic creates the opportunity to expand the research outline in this report by recruiting 30 additional subjects who can be scanned using an enhanced, high-resolution, Phillips Precedence SPECT/CT scanner. Further, the availability of DICOM software compatibility creates the possibility of performing computer-based fusion of SPECT/CT and radiation planning CTs. Computer-based fusion with dramatically enhance the rapidity and accuracy of creating SPECT/CT-informed standard treatment and IMRT plans.

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Appendix A
Revised Statement of Work

Task 1. Conduct a prospective cohort study to estimate the increased lymphedema risk associated with radiation therapy delivered to chest wall and lymph node beds.

Status: Subject Enrollment and data collection are complete. The work remaining to complete Task 1 is outlined below.

a) Review SPECT/CT scans (Months 1 - 3) – Dr. Cheville will review all follow-up scans to determine LN number and location. Additionally, 2 nuclear medicine radiologists will review the scans. Estimated completion date; 12/10/2008.

b) Data entry (Months 1 - 3) – Data entry will occur simultaneously with review of the SPECT CT scans. Estimated completion 12/10/2008.

c) Data analysis (Months 4 - 9) – Data cleansing and analysis will occur iteratively. The discovery of substantial lymphatic collateralization involving the axilla and supraclavicular lymph node beds has created the need for more sophisticated statistical analysis than initially anticipated. Estimated completion 6/10/2009.

d) Manuscript preparation (10 - 14) – It is anticipated that two manuscripts will be prepared. The first will examine the association between lymphedema and radiation delivered to all LNs and to the dominant LN. The second will describe lymphatic collateralization patterns and their association with lymphedema. Estimated completion 11/10/2009.

Task 2. Conduct a pilot study of 30 breast cancer patients requiring tangent beam breast irradiation in order to estimate reduction in LN radiation dose achievable through SPECT/CT-informed versus standard XRT planning. This study will further refine the technique developed through Dr. Cheville's previous work at the University of Pennsylvania by definitively addressing barriers to the integration of SPECT/CT-informed imaging into routine clinical practice. This study will have several aims all of which are designed to establish the utility of this technique for immediate application.

Status: The study has been approved by the Mayo Clinic Cancer Center Protocol Committee and Internal Review Board. All study forms have been developed and approved. All requisite personnel are currently available with time allocated to the project and have been appropriately trained.

a) Recruit 30 subjects (Months 1 - 20) – Using a conservative recruitment rate of 1.5 subjects per mo, we estimate that subject recruitment will be complete in 20 months. Estimated completion 04/01/2010.

b) Data Collection (Months 1 – 21) – Radiation simulation will occur within 1 week of study recruitment and SPECT/CT scans will be completed within 48 hours of radiation simulation. Computer-based image fusion of SPECT/CT scans and radiation simulation CT scans will be performed within 1 week of SPECT/CT scanning. Conventional and IMRT-based radiation treatment plans using the SPECT/CT fused images plans will be developed concurrent with SPECT/CT image fusion. Once treatment plans have been developed, the radiation doses delivered to LNs draining the arm can be immediately calculated. Data collection will occur concurrently with scanning. Although patients will be prospectively followed, the follow-up data does not pertain to the specific aims of this project. Therefore, data collection will be complete shortly after SPECT/CT scanning has been completed. Estimated completion 05/01/2010.

c) Data analysis (Month 22-23) – Data analysis will be relatively straightforward. Descriptive statistics will be performed regarding number and location of visualized LNs, as well as LN dosimetry with the 3 radiation treatment plans (conventional, SPECT/CT informed conventional, SPECT/CT-informed IMRT). ANOVA and student's T-tests will be used to compare mean LN dosimetry with the different treatment plans. Estimated completion 07/01/2010.

d) Manuscript preparation (Months 23 - 24) – A primary manuscript describing the degree of radiation dose reduction achieved with SPECT/CT-informed radiation planning will be prepared following data analysis. Additional manuscripts of lesser scope may be prepared during data collection. Estimated completion 09/01/2010.